METHOD AND SYSTEM TO INVESTIGATE A COMPLEX CHEMICAL SPACE

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BACKGROUND OF THE INVENTION

[0001] The present invention relates to a combinatorial high throughput screening method and system.

[0002] Combinatorial organic synthesis (COS) is a high throughput screening method that was developed for pharmaceuticals. COS uses systematic and repetitive synthesis to produce diverse molecular entities formed from sets of chemical "building blocks." As with traditional research, COS relies on experimental synthesis methodology. However instead of synthesizing a single compound, COS exploits automation and miniaturization to produce large libraries of compounds through successive stages, each of which produces a chemical modification of an existing molecule of a preceding stage. Libraries are physical, trackable collections of samples resulting from a definable set of the COS process or reaction steps. The libraries comprise compounds that can be screened for various activities.

[0003] Combinatorial high throughput screening (CHTS) is an HTS method that incorporates characteristics of COS. The CHTS methodology is marked by the search for high order synergies and effects of complex combinations of experimental variables through the use of large arrays in which multiple factors can be varied through multiple levels. Factors of an experiment can be varied within an array (typically formulation variables) and between an array and a condition (both formulation and processing variables). Results from the CHTS experiment can be used to compare properties of the products in order to discover "leads" – formulations and/or processing conditions that indicate commercial potential.

[0004] The steps of a CHTS methodology can be broken down into generic operations including selecting chemicals to be used in an experiment; introducing the chemicals into a formulation system (typically by weighing and dissolving to form stock solutions), combining aliquots of the solutions into formulations or mixtures in a geometrical array (typically by the use of a pipetting robot); processing the array of chemical combinations into products; and evaluating the products to produce results.

[0005] Typically, CHTS methodology is characterized by parallel reactions at a micro scale. In one aspect, CHTS can be described as a method comprising (A) an iteration of steps of (i) selecting a set of reactants; (ii) reacting the set and (iii) evaluating a set of products of the reacting step and (B) repeating the iteration of steps (i), (ii) and (iii) wherein a successive set of reactants selected for a step (i) is chosen as a result of an evaluating step (iii) of a preceding iteration.

[0006] Results from an experiment can be evaluated by aid of mathematical models as taught by G.E.P. Box and N. R. Draper, Empirical Model-Building and Response Surfaces, John Wiley and Sons, NY, 1987, p 20-22. The models can be used to find an approximation, typically a polynomial, to an unknown underlying theoretical function. For example, Taylor's Series expansion is a polynomial that can provide a valuable approximation of first or second order experimental interactions.

[0007] However, the study of catalyzed chemical reactions by CHTS involves the investigation of a complex experimental space characterized by multiple qualitative and quantitative factor levels. Typically, the interactions of a catalyzed chemical reaction such as a carbonylation reaction can involve interactions of an order of 6 or 9 or greater. While Taylor expansion approximation can be effectively applied to analyze first or second order interactions, it is useless to study CHTS results from a complex catalyzed chemical reaction.

[0008] Another problem is that catalyzed chemical reactions can be unpredictable. Well-known protocols in one area of chemistry cannot be applied to another area with assurance of success. For example, U.S. Pat. 6143914 shows that

some combinations of various metals unexpectedly increase a carbonylation catalyst turnover number (TON) and other related combinations do not. "Due to the complicated mechanistic nature of many transition metal based catalysts, structure - activity relationships are often unpredictable, leaving empirical exploration and serendipity the most common routes to discovery." J. Tian & G. W. Coates, Angew. Chem Int. Ed. 2000, 39, p 3626. This high degree of irregularity and unpredictability is illustrated in FIG.1.

[0009] There is a need for a methodology to examine the complex higher order and unpredictable interactions of a CHTS catalyzed chemical reaction experiment that cannot be examined by Taylor Series expansion or other standard methodology.

BRIEF SUMMARY OF THE INVENTION

[0010] The invention provides a particularly well-suited experimental methodology to investigate multiple and complex interactions of a catalyzed chemical reaction that involves both qualitative and quantitative factor levels. According to the invention, an experimental space of a catalyzed chemical reaction is defined to represent at least three factor interactions, a CHTS method is effected on the catalyzed chemical experimental space to produce results and results are analyzed according to matrix algebra to select a best case set of factor levels from the catalyzed experimental space.

[0011] In another embodiment, a CHTS experiment is conducted on a complex experimental space comprising qualitative and quantitative factors to produce first data results, (B) the first data results are analyzed according to matrix algebra, (C) a standard deviation of the analyzed results is defined, (D) data results that positively exceed the standard deviation are selected, (E) a next experimental space is defined according to the selected data results and (F) steps (A) through (E) are reiterated on the next experimental space until data results selected in step (D) represent satisfactory leads.

[0012] In yet another embodiment, a system for investigating a catalyzed experimental space, comprises a reactor for effecting a CHTS method on the catalyzed chemical experimental space to produce results and a programmed controller to analyze the results according to matrix algebra to select a best case set of factor levels from the catalyzed experimental space.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] FIG. 1 is a graphic representation of a complex catalyzed chemical experimental space;

[0014] FIG. 2 is a schematic representation of a CHTS system;

[0015] FIG. 3 shows representations of vector matrix forms; and

[00'6] FIG. 4 is a normal probability plot.

DETAILED DESCRIPTION OF THE INVENTION

[0017] A purpose of a CHTS experiment is to locate anomalies that represent high-value "leads." Leads are results that identify candidate factors and levels for a commercial process. According to the invention, matrix algebra is combined with CHTS to examine the very high-level interactions of a chemical catalytic reaction. In the CHTS/matrix algebra approach, a CHTS experiment in many factors can be run and then modeled to generate all main, 2nd, 3rd, 4th and even higher interactions. Suitably, the results can be represented according to a general linear model (GLM). A statistical analysis of the represented results determines high-order interaction leads.

[0018] In a typical CHTS method, a multiplicity of tagged reactants is subjected to an iteration of steps of (A) (i) simultaneously reacting the reactants, (ii) identifying a multiplicity of tagged products of the reaction and (B) evaluating the identified products after completion of a single or repeated iteration (A). A typical CHTS can utilize advanced automated, robotic, computerized and controlled loading, reacting and evaluating procedures.

[0019] The results from the CHTS experiment are analyzed using matrix algebra to extract combinations of the experiment interactions. A mathematical matrix is a representation of real numbers in a rectangular array. Matrices are important tools for expressing and discussing problems that may involve complex data sets. Matrix analysis is a multivariant methodology for expressing and manipulating these kinds of data and for solving problems posed by the data. Matrix operations can include representation (posing or modeling data in a matrix representation), addition, subtraction, scalar multiplication, matrix multiplication, multiplication by inverse, transposition (interchanging rows and columns) and distribution (assigning a probability value). Matrices can be manipulated to produce a sum, difference, scalar multiple, matrix multiple, product or transpose.

[0020] In the present invention, the matrices are representations of CHTS results in a rectangular array. The runs from the CHTS experiment provide sets of results or y's, one for each run, each correlated with a set of levels of factors, x_i . Each run y is associated with an error e. Each of the factors or interactions is associated with a coefficient β . These elements (x's, their interactions and y's) can be represented in vector/matrix form as shown in FIG. 3, wherein levels of factors and interactions form a rectangular array or matrix (20) of scalar values X. Further in FIG. 3, y's, β 's and e's are represented in single column matrices (10), (30), and (40). A matrix estimation equation of the system can be as follows:

$$y = X\beta + e$$
 (I)

[0021] where X is a matrix of factor and interaction levels in the experiment, y is a matrix of experimental results, β is effects (both main effects and interaction effects), every e_i in e has the same variance σ^2 , error terms e_i arise from a normal distribution and expected value E(y) (definition: the value of the response if no error is present) of the response is E(y) = X β .

[0022] The method involves solving the above matrix estimation equation (I), according to the relationship:

$$\beta = (X'X)^{-1}X'y \tag{II}$$

[0023] where superscript 'indicates a transpose of a matrix (in which each row becomes a column and each column a row). The superscript '1 indicates an inverse function of a matrix. Thus for any square matrix A, a relation can be defined as $AA^{-1} = I$, where I is the identity matrix 50 shown in the FIG. 3 model.

[0024] Accordingly, results can be assembled as an $n \times 1$ vector y and factor level values can be assembled into an $n \times k+1$ matrix X with 1's as designations in a first column and each other column containing the coded factor level values (+1's and -1's representing the extents of the values of the factors and interactions). Matrix equation (I) is then solved for effects parameters β .

[0025] The effects parameters of matrix β are then examined for statistical significance. The null hypothesis can be applied in this examination. The null hypothesis is that all of the effects observed in the experiment are caused simply by random processes. If this is correct, the effects will fit to a normal distribution and form a relatively straight line in a probability plot. In FIG. 4; E100 is a straight line representing a results approximation. The line is flanked by dashed lines denoting multiples of standard deviations. A desired standard deviation can be selected by an experimenter for the experiment. Any effects that fall off the line by more than the standard deviation can be interpreted to have been caused by nonrandom processes, as taught by D. Montgomery, Design and Analysis of Experiments, 3^{rd} Ed., John Wiley, 1991, NY, p 99. Effects that positively exceed the deviation can represent combinations that are failures or combinations that provide synergistic improvement, i.e., leads.

[0026] In a preferred embodiment, results from the CHTS method are analyzed by matrix algebra by steps of (A) representing the results as an n x 1 matrix y where n = a number of factor level combinations in the experiment, (B) representing extents of the factor level combinations in an n x n matrix X, (C) solving n

simultaneous equations represented by the matrices according to matrix algebra to form a results matrix β and (D) examining the results matrix β to identify effects outside a standard deviation.

[0027] The step (B) can comprise coding extents of the factor level combinations as a +1 or -1 and representing the coded extents as the n x 1 matrix y. The step (C) can comprise (i) transposing matrix X to form matrix X', (ii) postmultiplying X' by X to generate a matrix and (iii) postmultiplying the generated matrix by y to form the results matrix β . The step (D) can comprise (i) representing the results matrix β as a normal probability plot, defining a standard deviation for results of the plot and (iii) identifying positive interactions outside of the standard deviation. The standard deviation can represent a probability that a result deviation from the standard is random and that positive interactions can be identified outside of the deviation. In one embodiment, the probability can be established at 95 percent or better to define an experimental space for a commercial process or the probability can be established at 99.7 percent or better to define a best set of factor levels as leads for a commercial process.

[0028] In one embodiment, the invention is applied to screen for a catalyst to prepare a diaryl carbonate by carbonylation. Diaryl carbonates such as diphenyl carbonate can be prepared by reaction of hydroxyaromatic compounds such as phenol with oxygen and carbon monoxide in the presence of a catalyst composition comprising a Group VIIIB metal such as palladium or a compound thereof, a bromide source such as a quaternary ammonium or hexaalkylguanidinium bromide and a polyaniline in partially oxidized and partially reduced form.

[0029] Various methods for the preparation of diaryl carbonates by a carbonylation reaction of hydroxyaromatic compounds with carbon monoxide and oxygen have been disclosed. The carbonylation reaction requires a rather complex catalyst. Reference is made, for example, to Chaudhari et al., U.S. Pat. 5,917,077. The catalyst compositions described therein comprise a Group VIIIB metal (i.e., a

metal selected from the group consisting of ruthenium, rhodium, palladium, osmium, iridium and platinum) or a complex thereof.

[0030] The catalyst material also includes a bromide source. This may be a quaternary ammonium or quaternary phosphonium bromide or a hexaalkylguanidinium bromide. The guanidinium salts are often preferred; they include the \forall , T-bis(pentaalkylguanidinium)alkane salts. Salts in which the alkyl groups contain 2-6 carbon atoms and especially tetra-n-butylammonium bromide and hexaethylguanidinium bromide are particularly preferred.

[0031] Other catalytic constituents are necessary in accordance with Chaudhari et al. The constituents include inorganic cocatalysts, typically complexes of cobalt(II) salts with organic compounds capable of forming complexes, especially pentadentate complexes. Illustrative organic compounds of this type are nitrogenheterocyclic compounds including pyridines, bipyridines, terpyridines, quinolines, isoquinolines and biquinolines; aliphatic polyamines such as ethylenediamine and tetraalkylethylenediamines; crown ethers; aromatic or aliphatic amine ethers such as cryptanes; and Schiff bases. The especially preferred inorganic cocatalyst in many instances is a cobalt(II) complex with bis-3-(salicylalamino)propylmethylamine.

[0032] Organic cocatalysts may be present. These cocatalysts include various terpyridine, phenanthroline, quinoline and isoquinoline compounds including 2,2'.6',2"-terpyridine, 4-methylthio-2,2'.6',2"-terpyridine and 2,2'.6',2"-terpyridine Noxide,1,10-phenanthroline, 2,4,7,8-tetramethyl-1,10-phenanthroline, 4,7-diphenyl-1,10, phenanthroline and 3,4,7,8-tetramethy-1,10-phenanthroline. The terpyridines and especially 2,2'.6',2"-terpyridine are preferred.

[0033] Another catalyst constituent is a polyaniline in partially oxidized and partially reduced form.

[0034] Any hydroxyaromatic compound may be employed.

Monohydroxyaromatic compounds, such as phenol, the cresols, the xylenols and pcumylphenol are preferred with phenol being most preferred. The method may be

employed with dihydroxyaromatic compounds such as resorcinol, hydroquinone and 2,2-bis(4-hydroxyphenyl)propane or "bisphenol A," whereupon the products are polycarbonates.

[0035] Other reagents in the carbonylation process are oxygen and carbon monoxide, which react with the phenol to form the desired diaryl carbonate.

[0036] These and other features will become apparent from FIG. 2 and the following detailed discussion, which by way of example without limitation describe preferred embodiments of the present invention.

[0037] FIG. 2 is a schematic representation of a system 10 for CHTS according to the invention. FIG. 2 shows system 10 including dispensing assembly 12, reactor 14, detector 16 and controller 18. Further shown, is X-Y-Z robotic positioning stage 20, which supports array plate 22 with wells 24. The dispensing assembly 12 includes a battery of pipettes 26 that are controlled by controller 18. X-Y-Z robotic positioning stage 20 is controlled by controller 18 to position wells 24 of the array plate 22 beneath displacement pipettes 26 for delivery of test solutions from reservoirs 28.

[0038] Controller 18 controls aspiration of precursor solution into the battery of pipettes 26 and sequential positioning of the wells 24 of array plate 22 so that a prescribed stoichiometry and/or composition of reactant and/or catalyst can be delivered to the wells 24. By coordinating activation of the pipettes 26 and movement of plate 22 on the robotic X-Y-Z stage 20, a library of materials can be generated in a two-dimensional array for use in the CHTS method. Also, the controller 18 can be used to control sequence of charging of sample to reactor 14 and to control operation of the reactor 14 and the detector 16. Controller 18 can be a computer, processor, microprocessor or the like.

[0039] An experimental space definition defines the contents of the wells 24 for the CHTS method. The space can be defined according to any design that results in a representation of at least three factor interactions. Suitable designs include

fractional factorial design, Latin square design, Plackett-Burman design or Taguchi design. Preferably the design results in a representation of all interactions and preferably, the design is an orthogonal design such as a full factorial design. The design can be embodied as an algorithm or program resident in controller 18.

Controller 18 controls the sequence of charging array plate 22 into the reactor 14, which is synchronized with operation of detector 16. Detector 16 detects products of reaction in the wells 24 of an array plate 22 after reaction in reactor 14. Detector 16 can utilize chromotography, infra red spectroscopy, mass spectroscopy, laser mass spectroscopy, microspectroscopy, NMR or the like to determine the constituency of each reaction product. The controller 18 uses data on the sample charged by the pipettes 26 and on the constituency of reaction product for each sample from detector 16 to correlate a detected product with at least one varying parameter of reaction. Additionally, an algorithm or program can be resident in the controller 18 to represent the CHTS results according to a matrix form and to analyze the represented results by matrix algebra to determine leads.

[0041] As an example, if the method and system of FIG.1 is applied to study a carbonylation catalyst and/or to determine optimum carbonylation reaction conditions, the detector 16 analyzes the contents of the well for carbonylated product. In this case, the detector 16 can use Raman spectroscopy. The Raman peak is integrated using the analyzer electronics and the resulting data can be stored in the controller 18. Other analytical methods may be used - for example, Infrared spectrometry, mass spectrometry, headspace gas-liquid chromatography and fluorescence detection.

[0042] A method of screening complex catalyzed chemical reactions can be conducted in the FIG. 2 system 10. According to the method, catalyzed formulations are prepared according to any suitable procedure. For example, one procedure produces a homogeneous chemical reaction utilizing multiphase reactant systems. In this procedure, a formulation is prepared that represents a first reactant system that is at least partially embodied in a liquid. Each formulation is loaded as a thin film to a respective well 24 of the array plate 22 and the plate 22 is charged into reactor 14.

During the subsequent reaction, the liquid of the first reactant system embodied is contacted with a second reactant system at least partially embodied in a gas. The liquid forms a film having a thickness sufficient to allow the reaction rate of the reaction to be essentially independent of the mass transfer rate of the second reactant system into the liquid.

[0043] The method herein described can be used with any suitable catalyzed chemical reactant system. For example, the system and method herein can be used for determining a method for producing diphenyl carbonate (DPC). Diphenyl carbonate (DPC) is useful, inter alia, as an intermediate in the preparation of polycarbonates. One method for producing DPC involves the carbonylation of a hydroxyaromatic compound (e.g., phenol) in the presence of a catalyst system. A carbonylation catalyst system typically includes a Group VIII B metal (e.g., palladium), a halide composition and a combination of inorganic co-catalysts (IOCCs).

[0044] Generally, testing of new catalyst systems has been accomplished at macro-scale and, because the mechanism of this carbonylation reaction is not fully understood, the identity of additional effective IOCCs has eluded practitioners. An embodiment of the present invention allows a homogeneous carbonylation reaction to be carried out in parallel with various potential catalyst systems and, consequently, this embodiment can be used to identify effective IOCCs for the carbonylation of phenol.

[0045] The following Example is illustrative and should not be construed as a limitation on the scope of the claims unless a limitation is specifically recited.

EXAMPLE

[0046] This EXAMPLE illustrates an identification of an active and selective catalyst for the production of aromatic carbonates. The procedure identifies the best catalyst from a complex chemical space, where the chemical space is defined as an assemblage of all possible experimental conditions defined by a set of variable

parameters such as formulation ingredient identity or amount or process parameter such as reaction time, temperature, or pressure.

[0047] The chemical space consists of the following TABLE 1 chemical factor levels and TABLE 2 processing factor levels:

TABLE 1

Factor Primary Catalyst	Level Ru(acac)3 Pt(acac)2	Level All at 25 ppm
Metal Cocatalyst	Mn(acac)2 Fe(acac)3	150 and 1500 ppm
Cosolvent	Dimethylformamide (DMFA), Tetrahydrofuran (THF)	All at 10%
Anion Cocatalyst	Cl', Br', (as hexamethylguanadinium salts)	All at 5000 ppm
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TABLE 2

Factor Level

Pressure 1000 psi, 1500 psi (8% Oxygen in Carbon Monoxide)

Temperature 100 C, 120 C

[0048] The system has seven factors, each at two levels. There are 2^7 = 128 possible combinations of these levels. The experiment is set up according to a full factorial design with 128 runs as shown in TABLE 3. In the experiment, catalyzed mixtures are made up in phenol solvent using the concentrations of each component as given in the rows of TABLE 3. The total volume of each catalyzed mixture is 1.0 ml. From each mixture, a 25 microliter aliquot is dispensed into a 2 ml reaction vial, forming a film on the bottom. The vials are grouped in array plates by process conditions (as specified in the Pressure and Temperature columns in the table) and each array plate is loaded into a high pressure autoclave and subjected to the reaction conditions specified. At the end of the reaction time, the reactor is cooled and depressurized and the contents of each vial are analyzed for diphenyl carbonate

product using a gas chromatographic method. A turnover number (TON) for each reaction is calculated as mols of diphenylcarbonate/mols of primary catalyst. The results are given in the TON column of TABLE 3.

TABLE 3

		C:					
A:	B:	Metal		E:			
Primary	Metal	Cocatalyst	D:	Anion	F:	G:	
Catalyst	Cocatalyst	Amount	Cosolvent	Cocatalyst	Pressure	Temp.	TON
Pt	Mn	150	DMFA	Br	1000	100	3340
Ru	Mn	150	DMFA	Br	1000	100	3470
Pt	Fe	150	DMFA	Br	1000	100	2360
Ru	Fe	150	DMFA	Br	1000	100	2260
Pt	Mn	1500	DMFA	Br	1000	100	2310
Ru	Mn	1500	DMFA	Br	1000	100	2060
Pt	Fe	1500	DMFA	Br	1000	100	3030
Ru	Fe	1500	DMFA	Br	1000	100	3200
Pt	Mn	150	THF	Br	1000	100	2430
Ru	Mn	150	THF	Br	1000	100	2270
Pt	Fe	150	THF	Br	1000	100	2910
Ru	Fe	150	THF	Br	1000	100	3160
Pt	Mn	1500	THF	Br	1000	100	3270
Ru	Mn	1500	THF	Br	1000	100	3030
Pt	Fe	1500	THF	Br	1000	100	2260
Ru	Fe	1500	THF	Br	1000	100	2470
Pt	Mn	150	DMFA	Cl	1000	100	3040
Ru	Mn	150	DMFA	Cl	1000	100	3340
Pt	Fe	150	DMFA	Cl	1000	100	2030
Ru	Fe	150	DMFA	Cl	1000	100	1860
Pt	Mn	1500	DMFA	Cl	1000	100	2200
Ru	Mn	1500	DMFA	Cl	1000	100	1920
Pt	Fe	1500	DMFA	Cl	1000	100	3290
Ru	Fe	1500	DMFA	Cl	1000	100	2910
Pt	Mn	150	THF	C1	1000	100	2260
Ru	Mn	150	THF	Cl	1000	100	2410
Pt	Fe	150	THF	Cl	1000	100	3260
Ru	Fe	150	THF	C1	1000	100	3200
Pt	Mn	1500	THF	C1	1000	100	3360
Ru	Mn	1500	THF	Cl	1000	100	3090
Pt	Fe	1500	THF	Cl	1000	100	2320
Ru	Fe	1500	THF	Cl	1000	100	2320
Pt	Mn	150	DMFA	Br	1500	100	3230
Ru	Mn	150	DMFA	Br	1500	100	3710
Pt	Fe	150	DMFA	Br	1500	100	2140
Ru	Fe	150	DMFA	Br	1500	100	2500
Pt	Mn	1500	DMFA	Br	1500	100	2490
Ru	Mn	1500	DMFA	Br	1500	100	2230
Pt	Fe	1500	DMFA	Br	1500	100	3070

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Ru	Fe	1500	DMFA	Br	1500	100	3360
Pt	Mn	150	THF	Br	1500	100	2680
Ru	Mn	150	THF	Br	1500	100	2640
Pt	Fe	150	THF	Br	1500	100	3520
Ru	Fe	150	THF	Br	1500	100	3620
Pt	Mn	1500	THF	Br	1500	100	3620
Ru	Mn	1500	THF	Br	1500	100	3830
Pt	Fe	1500	THF	Br	1500	100	2710
Ru	Fe	1500	THF	Br	1500	100	2580
Pt	Mn	150	DMFA	Cl	1500	100	3310
Ru	Mn	150	DMFA	Cl	1500	100	3740
Pt	Fe	150	DMFA	Cl	1500	100	2460
Ru	Fe	150	DMFA	Cl	1500	100	2410
Pt	Mn	1500	DMFA	Cl	1500	100	2020
Ru	Mn	1500	DMFA	C1	1500	100	2300
Pt	Fe	1500	DMFA	C1	1500	100	3270
Ru	Fe	1500	DMFA	Cl	1500	100	3250
Pt	Mn	150	THF	C1	1500	100	2800
Ru	Mn	150	THF	C1	1500	100	2520
Pt	Fe	150	THF	Cl	1500	100	3850
Ru	Fe	150	THF	Cl	1500	100	3570
Pt	Mn	1500	THF	Cl	1500	100	3540
Ru	Mn	1500	THF	Cl	1500	100	3950
Pt	Fe	1500	THF	Cl	1500	100	2730
Ru	Fe	1500	THF	C1	1500	100	2520
Pt	Mn	150	DMFA	Br	1000	120	3300
Ru	Mn	150	DMFA	Br	1000	120	3800
Pt	Fe	150	DMFA	Br	1000	120	2640
Ru	Fe	150	DMFA	Br	1000	120	2520
Pt	Mn	1500	DMFA	Br	1000	120	2220
Ru	Mn	1500	DMFA	Br	1000	120	2270
Pt	Fe	1500	DMFA	Br	1000	120	3960
Ru	Fe	1500	DMFA	Br	1000	120	3360
Pt	Mn	150	THF	Br	1000	120	2560
Ru	Mn	150	THF	Br	1000	120	2440
Pt	Fe	150	THF	Br	1000	120	3560
Ru	Fe	150	THF	Br	1000	120	3620
Pt	Mn	1500	THF	Br	1000	120	3650
Ru	Mn	1500	THF	Br	1000	120	3570
Pt	Fe	1500	THF	Br	1000	120	2650
Ru	Fe	1500	THF	Br	1000	120	2710
Pt	Mn	150	DMFA	Cl	1000	120	3380
Ru	Mn	150	DMFA	Cl	1000	120	3430
Pt	Fe	150	DMFA	C1	1000	120	2480
Ru	Fe	150	DMFA	C1	1000	120	2310
Pt	Mn	1500	DMFA	Cl	1000	120	2510

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Ru	Mn	1500	DMFA	C1	1000	120	2410
Pt	Fe	1500	DMFA	Cl	1000	120	3320
Ru	Fe	1500	DMFA	Cl	1000	120	3620
Pt	Mn	150	THF	C1	1000	120	2880
Ru	Mn	150	THF	Cl	1000	120	2430
Pt	Fe	150	THF	Cl	1000	120	3940
Ru	Fe	150	THF	Cl	1000	120	4290
Pt	Mn	1500	THF	C1	1000	120	3730
Ru	Mn	1500	THF	C1	1000	120	3730
Pt	Fe	1500	THF	Cl	1000	120	2730
Ru	Fe	1500	THF	Cl	1000	120	2480
Pt	Mn	150	DMFA	Br	1500	120	3510
Ru	Mn	150	DMFA	Br	1500	120	3420
Pt	Fe	150	DMFA	Br	1500	120	2340
Ru	Fe	150	DMFA	Br	1500	120	2390
Pt	Mn	1500	DMFA	Br	1500	120	2210
Ru	Mn	1500	DMFA	Br	1500	120	2660
Pt	Fe	1500	DMFA	Br	1500	120	3270
Ru	Fe	1500	DMFA	Br	1500	120	3550
Pt	Mn	150	THF	Br	1500	120	2450
Ru	Mn	150	THF	Br	1500	120	2830
Pt	Fe	150	THF	Br	1500	120	3910
Ru	Fe	150	THF	Br	1500	120	3850
Pt	Mn	1500	THF	Br	1500	120	3470
Ru	Mn	1500	THF	Br	1500	120	3730
Pt	Fe	1500	THF	Br	1500	120	2360
Ru	Fe	1500	THF	Br	1500	120	2660
Pt	Mn	150	DMFA	Cl	1500	120	3640
Ru	Mn	150	DMFA	CI	1500	120	3440
Pt	Fe	150	DMFA	Cl	1500	120	2380
Ru	Fe	150	DMFA	C1	1500	120	2230
Pt	Mn	1500	DMFA	Cl	1500	120	2510
Ru	Mn	1500	DMFA	C1	1500	120	2150
Pt	Fe	1500	DMFA	C1	1500	120	3100
Ru	Fe	1500	DMFA	Cl	1500	120	3810
Pt	Mn	150	THF	Cl	1500	120	2380
Ru	Mn	150	THF	C1	1500	120	2900
Pt	Fe	150	THF	Cl	1500	120	3740
Ru	Fe	150	THF	C1	1500	120	3620
Pt	Mn	1500	THF	Cl	1500	120	3610
Ru	Mn	1500	THF	Cl	1500	120	3680
Pt	Fe	1500	THF	C1	1500	120	2570
Ru	Fe	1500	THF	C1	1500	120	2880

[0001] Analysis of the data using matrix estimation formula (I) gives the information of TABLE 4. The Terms are the main effects and interactions of the factors in TABLE 3 and A-F are as given in the heading of TABLE 3. Thus A is the main effect of Factor "Primary Catalyst" and AD is the interaction effect of the Factors "Primary Catalyst" and "Cosolvent." Effects are β s.

Table 4

Term Effect (9) Term Effect (9) Term A 25 BFG 22 ABDEF B 2 CDE 24 ABDEG C -43 CDF -114 ABDFG D 164 CDG 1 ABEFG E 32 CEF -67 ACDEF F 20 CEG 20 ACDEF G 229 CFG 11 ACEFG AC 2 DFG 12 ACEFG AC 2 DFG 13 ACEFG AC 2 DFG 40 -16 ACEFG AC 2 ABC -52 BCDEG AF -26 ABC -52 BCDEG AF -26 ABC -52 BCDEG BD 29 ABCG 30 CDEFG BE 73 ABCG 40 BDEFG BE 73 ABDE 44 ABCDEFG BF 16 ABDF 13 ABCDEG BF 16 ABDF 13 ABCDEG BF 16 ABDF 13 ABCDEG C ABCG -12 ABCDEG 11 ABCDEG C ABCG -12 ABCDEG 21 ABCDEG C ABCG -12 ABCDEG 21 ABCDEG C ABCG -12 ABCDEG 21 ABCDEG C ABCG -27 ACDEG 21 ABCDEG C ABCG -27 ACDEG 21 ABCDEG C -28 ABEG -11 ABCDEG C -27 ACDEG -4 ABCDEG -4 ABCDEG C -28 ABEG -11 ABCDEG C -27 ACDEG -4 ABCDEG -4 ABCDEG C -28 ABEG -11 ABCDEG C -29 ACCE -21 ABCDEG -4 ABCDEG C -27 ACDEG -4 ABCDEG -4 ABCDEG C -28 ABEG -20 ACDEG -4 ABCDEG C -27 ACDEG -4 ABCDEG -4 ABCDEG C -28 ABEG -20 ACDEG -4 ABCDEG C -27 ACDEG -4 ABCDEG -4 ABCDEG C -28 ABEG -20 ACDEG -4 ABCDEG C -27 ACDEG -4 ABCDEG -4 ABCDEG C -28 ABEG -4 ABCDEG -4 ABCDEG C -27 ACDEG -4 ACDEG -4 ABCDEG C -28 ABCG -4 ABCDEG -4 ABCDEG C -27 ACDEG -4 ACDEG -4 ABCDEG C -28 ABCG -4 ACDEG -4 ABCDEG -4 ABCDEG C -29 ACCE -4 ACCE -4 ABCDEG -4	
A .25 Beg	Effect (β)
B 2 CDE -24. ABDEG C -43 CDF -14. ABDEG D -164 CDG -1 ABEFG E -32 CEG -20 ACDEF E -32 CEG -20 ACDEF G -20 CGG -20 ACDEF G -20 CGG -20 ACDEG G -20 CGG -11 ABEFG G -20 CGG -11 ABEFG AC -2 DEG -15. ADDEG AC -2 ADFG -37.3 BCDEG AC -2 BCDEG AC -2 BCDEG -37.3 BCDEG AC -2 ABC -32 BCDEG AC -42 ABCG -52 BCDEG BC -39 ABCG -30 CDEG BC -39 ABCG -30 CDEG BE -16 ABDEG -13 ABCDEG BE -73 ABDEG -14 ABCDEG BE -73 ABDEG -13 ABCDEG BC -29 ABCG -12 ABCDEG CC -27 ABCG -11 ABCDEG CC -28 ABEG -11 ABCDEG CC -27 ACDEG -11 ABCDEG CC -27 ACDEG -20 ACDEG CC -20 ADEG -1 ABCDEG ABCG -18 BCDEG -1 ABCDEG ABCG -18 BCDEG -1 ABCDEG -1 ABCDEG ABCG -18 BCDEG -1 ABCDEG -1 ABCDEG ABCG -18 BCDEG -20 ACCG -20 BC	-24
C 43 CDF 1-14 ABDFG D 164 CDG 1 ABEFG E 32 CEF -67 ACDEF F 20 CEG 20 ACDEG G 229 CFG 13 ACDEG AB 10 DEF 15 ACDEG AB 10 DEF 16 ACDEG AB 10 DEF 16 ACDEG AC 2 DEG 16 ACDEG AC 2 DEG 17 BCDEG AC 2 DEG 18 ACDEG AC 2 BFG 37.5 BCDEG AB 22 BCG 39 ACDEG BC 39 ABCG 30 BDEG BC 39 ABCG 30 BDEG BC 39 ABCG 30 ACDEG BE 73 ABDE 44 ACDEG BE 73 ABDE 13 ACDEG BC 28 ABEG 13 ABCDEG BC 28 ABEG 13 ABCDEG CC 28 ABEG 13 ABDEG CC 27 ACDE 4 BCDEFG CC 27 ACDE 12 BCDEFG CC 27 ACDE 12 BCDEFG CC 21 ABCD 12 ABCDEFG CC 21 ABCD 12 ABCDEFG ABC 21 ADEG 11 ACDG 12 ABCDEFG ABC 21 ADEG 21 ABCDEFG ABC 21 ADEG 21 ABCDEFG ABC 21 ADEG 21 ABCDEFG ABC 21 ADEG 22 ABCDEFG ABC 21 ADEG 22 ABCDEFG ABC 21 ADEG 22 ACDEFG ABC 21 ADEG 22 ABCDEFG ABC 22 ABCDEFG ABC 21 ADEG 22 ABCDEFG ABC 23 ABCDEFG ABC 22 ABCDEFG ABCDEFG ABCDEFG AB	-7
D 164 CDG 1 ABEFG E 32 CEF 67 ACDEF F 20 CEG 20 ACDEG G 229 CFG 11 ACDEG AC 2 DEG 14 ACDEG AC 2 DEG 16 ADEG AC 2 DEG 17 BEFG ACC 37 BEFG ACC 37 BEFG ACC 30 ADC ACC 42 ABCG BC 22 ABCG BC 23 ABCG BC 30 CDEG BC BC 29 ABCG BC 13 ABCG BC 13 ABCG BC 13 ABCG BC 13 ABCG CC 21 ABCD CC 21 ABCD CC 23 ABCG CC 24 ACDC CC 25 ACDC CC 25 ACDC CC 26 ABCG CC 27 ACDC CC 27 ACDC CC 28 ABCG CC 27 ACDC CC 28 ABCG CC 27 ACDC CC 27 ACDC CC 28 ABCG CC 27 ACDC CC 27 ACDC CC 28 ABCG CC 27 ACDC CC 27 ACDC CC 28 ABCG CC 27 ACDC CC 27 ACDC CC 27 ACDC CC 27 ACDC CC 28 ABCG CC 21 BCC CC 21 BCC CC 22 ACDC CC 24 ACDC CC 24 ACDC CC 25 ACCC CC 26 ACCC CC 27 ACDC CC 27	-58
E 32 CEF -67 ACDEF F 20 CEG 20 ACDEG G 229 CFG 13 ACDEG AB 10 DEF 11 ACDEG AB 10 DEF 11 ACDEG AC 2 DEG -16 ADEFG AD 7 DEG -16 ADEFG AD 7 DEG -17 BCDEG AB 22 BC -17 BCDEG AB 23 BCDEG AB 24 AB CF -24 BCDEG BC 39 AB CF -40 BDEFG BC 39 AB CF -40 BDEFG BC 39 AB CF -10 AB CDEG BC -25 AB CFG AB BC -11 AB CDEG BC -28 AB CF -11 AB CDEG BC -28 AB CFG CF -28 AB CFG CF -28 AB ACDEG ACDEFG ACDEG ACDEFG ACDEG ACDEFG ACDEG ACDEFG ACDEG -11 AB CDEFG ACDEG -12 AB CDEFG ACDEG -11 AB CDEFG ACDEG -12 AB CDEFG ACDEG -11 AB CDEFG ACC -21 AD AD CDEG -1 AB CDEFG ACC -21 AD AD CDEG -1 AB CDEFG ACC -21 AD CDC -1 AB CDC -	9
F 20 CEG 20 ACDEG G 229 CFG 13 ACDEG AB 10 DEF 11 ACDEG AC 2 DEG 1-16 ADEFG AC 2 DEG 40 BCDEG AC 2 DEG 40 BCDEG AC 2 DEG 40 BCDEG AC 2 BCG 3-75 BCDEG AC 2 BCG 3-75 BCDEG AC 3-2 BCG 3-75 BCDEG AC 42 ABCC 2 BCG 3-75 BCDEG BC 3-9 ABCG 30 CDEG BC 39 ABCG 30 CDEG BC 39 ABCG 30 CDEG BC 30 ABC 31 ABCD BC 30 ABC 13 ABCD BC 30 ABCD 13 ABCDEG BC 41 ABCD 13 ABCDEG BC 40 ABCD 13 ABCDEG BC 40 ABCD 13 ABCDEG CC 27 ACDE 11 ABCDEG CC 23 ABCG 10 ACDEG CC 23 ABCG 12 ABCD CC 24 ACDEG 12 ABCDEG CC 25 ACDEG 12 ABCDEG CC 27 ACDE 12 ABCDEG CC 27 ACDE 21 ABCDEG CC 28 ABCG 12 ABCDEG CC 27 ACDEG 21 ABCDEG CC 27 ACDE 22 ACDEG CC 27 ACDE 22 ACDEG CC 27 ACDE 22 ACDEG 22 ABCDEG CC 3-3 ACDEG 12 BCDEG CC 3-3 ACDEG 12 BCDEG CC 3-3 ACDEG 12 BCDEG CC 3-3 ACDEG 12 ABCDEG CC 3-3 ACDEG 12 BCDEG CC 3-3 ACDEG 12 BCDEG CC 3-4 ACDEG 12 BCDEG CC 3-5 ACDEG 14 ACDEG 14 ABCDEG CC 3-6 ABCG 32 BCDEG CC 3-7 ACDEG 32 BCDEG CC 3-7 ACDEG 32 BCDEG CC 3-8 ACCG 32 BCDEG 44 ACCG 32 BCDEG	+25
G 229 CFG 13 ACDFG AB 10 DEF 1.6 ACDFG AC 2 DEG -1.6 ADEFG AC 2 DEG -1.6 ADEFG AD 7 DFG -1.6 ADEFG AD 7 DFG -1.6 ADEFG AE 22 EFG -37.3 BCDEG AF -2.6 ABCD -32.3 BCDEG AG 42 ABCE -32 BCDFG BC 39 ABCB -30 BCDFG BC 39 ABCB -30 BCDFG BE 73 ABDG 10 CFG BE 73 ABDG 11 ABCDFG BE 73 ABDG 13 ABDG ABCB BC -1.1 ABCDFG BC -2.2 ABGG 13 ABCB BC -2.2 ABGG 13 ABCB BC -2.2 ABFG 13 ABCB BC -2.2 ABFG 13 ABCB BC -2.2 ABBG 13 ABCB BC -2.2 ABBG 13 ABCBFG BC -2.3 ABFG 12 ABCBFG BC -2.3 ABFG 20 ACDEFG BC -2.3 ABFG 20 ACDEFG BC -2.3 ABBG 13 ABCBFG BC -2.3 ABCBFG -1.1 ABCBFG BC -2.3 ABCG -2.1 ABCBFG BC -2.2 ACDF -2.2 ABCDFG BC -2.2 ABCBFG -1.1 ABCDFG BC -2.2 ABCBFG -1.1 ABCBFG BC -2.2 ABCBFG -1.1 ABCBFG BC -2.2 ABCBFG -1.1 ABCGFG -1.1 A	22
AB 10 DEF 1 ACEFG AC 2 DEG 16 ADEFG AD 7 DEG 46 BCDEF AE 22 BC ABCD 2 BCDEF AF -26 ABCD -2 BCDEF AG 42 ABCD -2 BCDEF AG 32 BCDEF BC 33 ABCG -30 CDEFG BE 16 ABDF 13 ABDEFG BC ABCD -12 ABCDEF BC ABCD -13 ABCDEF BC ABCD -14 ABCDEF CC -28 ABCD -11 ABCDEFG CC -23 ABCD -11 ABCDEFG CC -23 ABCD -11 ABCDEFG CC -23 ABCD -12 ABCDEFG CC -25 ACDEF -12 ABCDEFG CC -26 ABCD -12 ABCDEFG CC -27 ACDE -12 ABCDEFG CC -27 ACDE -12 ABCDEFG CC -28 ABCD -12 ABCDEFG CC -28 ABCD -12 ABCDEFG CC -27 ACDE -22 ABCDEFG CC -28 ABCD -12 ABCDEFG CC -27 ACDE -21 ABCDEFG CC -28 ABCD -21 BCDEFG CC -28 ABCD -21 BCDEFG CC -29 ACCD -21 BCDEFG CC -20 ACCDEFG CC -20 ACCDEFG CC -21 ABCDEFG CC -22 ACCDE -24 ABCDEFG CC -24 ABCDEFG CC -25 ACCDE -24 ABCDEFG CC -26 ABCDEFG CC -27 BCDEFG CC -23 BDEFG CC -27 BCDEFG CC -24 ABCDEFG CC -27 BCDEFG CC -24 ABCDEFG CC -27 BCDEFG CC -27 BCDEFG CC -27 BCDEFG CC -23 BDEFG CC -24 ABCDEFG CC -27 BCDEFG CC -24 ABCDEFG CC -27 BCDEFG CC -27 BCDEFG CC -27 BCDEFG CC -23 BDEFG CC -24 ABCDEFG CC -27 BCDEFG CC -24 ABCDEFG CC -24 ABCDEFG CC -25 BCDEFG CC -25 ABCDEFG C	-16
AC 2 DEG -16. ADEFG AD 7 DFG 40 ADEFG 40 ADEFG 40 ADEFG 40 ADEFG 37. BCDEFG AF -26 ABCDE -22 BCDFG AG 42 ABCC -22 BCDFG BC 39 ABCC -30 DCGG BD 29 ABCC -30 DCGG BE 73 ABDC -11 ABCDEG BE 73 ABDC -11 ABCDEG BG -12 ABDC -11 ABCDFG CG -23 ABGG -13 ABGC -11 ABCDFG CF -23 ABGG -13 ABGG -11 ABCDFG CF -24 ABCG -27 ACDE -4 BCCDFG DF -31 ACDF -22 ABCDFG BF -9 ACDF -22 ABCDFG FG -188 ADDF -7 ABCDFG FG -188 ADDF -7 ABCDFG ABC -21 ADFG -11 ABCDFG ABC -21 ADFG -1 ABCDFG -1 ABCDFG ABC -21 ADFG -1 ABCDFG -1 ABCDFG -1 ABCDFG -1 ABCDFG -1 ABCDFG -1 ABCG -1 ABCGG -1 ABCGGG -1 ABCGGG -1 ABCGGG -1 ABCGGG -1 ABCGGG -20 ACCGG -20 ABCGGG -20 ACCGG -20 ABCGGG -20 ACCGG -20 ABCGGG -20 ACCGGG -20 ACCGGG -20 ACCGGG -20 ACCGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG	51
AD 7 DFG 40" BCDEF AE 22 ER ABCD 32 BCDEG AF -26 ABCD 32 BCDEG AG 42 ABCD 32 BCDFG BC 39 ABCG 30 CDEFG BE 29 ABCG 30 ABCD 13 ABCDEFG BE 73 ABCD 13 ABCDEFG BC 39 ABCD 13 ABCDEFG BC 39 ABCD 13 ABCDEFG BC 30 ABCD 13 ABCDEFG BC 30 ABCD 13 ABCDEFG BC 30 ABCD 13 ABCDEFG BC 31 ABCDEFG CC 21 ABCDEFG CC 23 ABCG 13 ABCG CC 23 ABCG 12 ABCDEFG CC 23 ABCG 20 ACDEFG CC 23 ABCG 20 ACDEFG CC 23 ABCG 20 ACDEFG CC 25 ABCD 21 ABCDEFG CC 25 ABCDEFG CC 25 ABCDEFG CC 25 ABCDEFG CC 26 ABCDEFG CC 27 ACDE 40 ACDEFG CC 27 ACDEFG CC 26 ABCDEFG CC 27 ACDE 40 ACDEFG CC 27 ACDEFG CC 28 ABCG CC 28 ABCG CC 24 ABCG CC 27 ACDEFG C	-6
AE 22 BFG -37.3 BCDEG AF -26 ABCD 2 BCDFG AG 42 ABCE -52 BCDFG BC 39 ABCF -40 BDEEG BD 29 ABCG 30 CDEEG BE 73 ABDE 11 ABCDEG BF 16 ABDE 11 ABCDEG CC -28 ABC -11 ABCDEG CC -28 ABC -11 ABCDEG CC -28 ABCG -12 ABCCFG CC -27 ACCFG -2 ABCGFG CC -27 ACCFG -22 ABCCFG DE 31 ACCFG -4 ABCCFG DE 31 ACCFG -4 ABCCFG DE 31 ACCFG -4 ABCCFG DE 31 ACCFG -1 ABCCFG DF -3 ACCFG -22 ABCCFG DF -3 ACCFG -22 ABCCFG ABCG -11 ABCCFG ABCG -11 ABCCFG ABCG -11 ABCCFG ABCG -11 ABCCFG -1 ABCCFG ABCG -21 ABCCFG -1 ABCCFG ABC -21 ABCGFG -1 ABCCFG ABC -21 ABCGFG -1 ABCGFG	3
AF	21
AG 42 ABGC -32 BCEFG BC 39 ABGC 30 CDEFG BD 29 ABGG 30 CDEFG BE 73 ABDE 11 ABCDEFG BF 16 ABDF 11 ABCDEFG BG -12 ABCFG 11 ABCDEFG CC -28 ABFG 11 ABCDEFG CC -28 ABFG 20 ABCFG CC -27 ACDE 4 BCDEFG DB 23 ABCG 12 ABCFG DB 23 ACDE 4 BCDEFG DB 23 ACDE 4 BCDEFG DF 25 ACCF 21 ABCDEFG DF 31 ACCF 40 ACCF DF 31 ACCF 41 ACCF DF 31 ACCF 41 ACCF DF 31 ACCF 41 ACCF ABC 21 ADCFG 41 ACCF ABC 41 ACCF 41 ACCF ABC 41 ACCF 41 ACCF ABC 41 BCCF 41 ACCF ACCF 27 BCCFG 6 ACCF 27 BCCFG 73 ACCFG 73 AC	-40
BCC 39 ABCF -40- BDEFG 30 CDEFG BE 73 ABDC 30 CDEFG BF 16 ABDF 13 ABDEFG BG -12 ABDG 21 ABCDFG CC ABEF -11 ABCDFG CC -28 ABEG 13 ABCFG CC -28 ABEG 13 ABDEFG CC -27 ACDE 4 BCDFG CC -27 ACDE 4 BCDFG CC -27 ACDE 4 BCDFG CC -27 ACDE 24 BCDFG CC -27 ACDE 22 ABCFG CC -27 ACDE 24 BCDFG CC -27 ACDE 24 BCDFG CC -27 ACDF -40 DF -31 ACDFG 12 DF -40 ACDFG 12 DF -40 ABCDFG ABC -21 ADDFG -41 ABC -21 ADFG -41 ABC -21 BCCG -41 ABCG -22 BCCG -6 ADFG -6 ADFG -6 ADFG -6 ADFG -6 ADFG -6 ADFG -32 ACFG -33 BCFG -33 ACFG	9
BD	-26
BE 73 ABDE 44- ABCDEF BF 16 ABDF 13 . ABCDEG BG -12 ABDF 21 ABCDEG CD 6 ABEF -11 . ABCDEG CC -28 ABEG 13 . ABCDEG CC -27 ACDE 4 . BCDEF CC -28 ACDE 21 CC -21 ACDE 21 CC -22 ACDE 21 CC -22 ACDE 21 CC -23 ACDE 21 CC -24 ADBO 41 ABD 13 ACDF 12 ABD 13 ACDF 4 ABD 13 ACDF 4 ABE -6 BCDE 56 ABF 4 BCDF 14 ABE -6 BCDE 56 ABF 4 BCDF 14 ACD -14 BCDF 14 ACD -14 BCDF 24 ACC 1 BCDF 24 ACC 1 BCDF 6 ACC 1 BCDF 12 ACC 1 BCDF 13 ACC 1 BCDF 14 ACC 1 BCDF 15 ACC 1 BCD	18
BF 16 ABDF 13 - ABCDEG BG -12 ABDO 21 ABCDEG CC -28 ABEG 11 - ABCEG CF 23 ABEG 20 ACDEFG CG -27 ACDE 28 ACDE -22 ABCDEG DF -31 ACDE -22 ABCDEG DF -35 ACDE -22 ABCDEG DF -35 ACDE -22 ABCDEG DF -35 ACDE -24 ABCDEG DG -35 ACDE -40 DG -35 ACDE -40 DG -35 ACDE -41 DG -35 ACDE -40 ABCDEG -21 BF -9 ACDE -7 BC -22 ACDE -7 BC -23 ACDE -7 BC -24 ABCDEG -1 ACCE -1 BCDEG -1	51
BG	1
ABEF -11 - ABCEFG CE -28 ABEG 13 - ABDEFG CF 23 ABEG 20 ACDEFG CG -27 ACDE -4 BCDEFG DE 28 ACDF -22 - ACDEFG DF -31 ACDE -40 DG -35 ACDE -40 DG -35 ACDE -40 DG -35 ACDE -40 A	20
CE 2-8 ABEG 13 ABEG CF 20 ACDEFG CF 23 ABEG 20 ACDEFG CG 2-7 ACDE 4 BCDEFG CG 2-7 ACDE 22 ACDE 22 ACDE 22 ACDE 22 ACDE 22 ACDE 23 ACDE 22 ACDE 24 ACDE 24 ACDE 24 ACDE 24 ACDE 24 ACDE 24 ACDE 25 ACDE 27 ACDE 24 ACDE 27 ACDE 24 ACDE 24 ACDE 24 ACDE 24 ACDE 25 ACDE 25 ACDE 26 ACDE 26 ACDE 27 ACDE 26 ACDE 27 ACDE 26 ACDE 27 ACDE 26 ACDE 27 ACDE	-73
ABFG 20 ACDEFG CG 23 ACDE 4 BCDEFG CG 27 ACDE 4 BCDEFG CG 27 ACDE 22 ABCDEFG DF 31 ACDF 12 ABCDEFG DF 31 ACDF 40 DF 31 ACDF 40 DF 31 ACDF 40 DF 31 ACDF 40 DF 41 ABCDEFG DF 41 ABCDEFG DF 42 ABCDEFG DF 42 ABCDEFG DF 44 ABCD 41 ABCD	-57
CG -27 ACDE 4 BCDEFG DE 28 ACDF -22 7 ABCDEFG DF -31 ACDG 12 DG -35 ACDF -40 EF -9 ACDG 21 EG -25 ACDG -32 FG -188 ADEF 7 ABC -21 ADEG -1 ABD 13 ADEG -2 ADEG -25 ACDG -2 ADEG -2 ACDG -2 ADEG -2 ACDG -2 ADEG -2 ACDG -2 ACDG -20 BDCFG -8 ACCG -27 BCCG -6 ACCG -27 BCCG -6 ACCG -20 BDCF -6 ACCG -20 BDCFG -3 ACCG -3 A	-4
ACDF -22 7 ABCDEFG DF -31 ACDF -12 7 DF -31 ACDF -40 DF -35 ACDG -12 DF -35 ACDG -21 DF -35 ACDG -32 DF -35 ACDG -41 ADD -18 ADDG -41 ADD -13 ADDG -1 ADD -14 ADDG -56 ADD -14 BCDF -14 ACD -17 BCDG -24 ACD -17 BCDG -25 ACD -20 BCDG -6 ADD -17 BDDG -12 ADD -17 BDDG -12 ADD -17 BDDG -32 ADD -33 BEFG -30 ADD -31 CDDE	4
DE 41 ACDG 12 DE 41 ACDG 12 DE 50 ACEF -40 DE 61 -50 ACEF -40 DE 7 9 ACEG 21 DE 62 -25 ACEG 21 ADE 7 ACEG 41 ADE 7 ADEG 41 ADE 13 ADEG 41 ADE 64 AEEG -56 ABF 4 BCDE -56 ABF 4 BCDE -56 ABF 4 BCDE -56 ACC 11 BCDE 24 ACD -14 BCDE 24 ACD -14 BCDE 25 ACE 1 BCEG 29 ACE 1 BCEG 6 ACE 1 BCEG 6 ACE 27 BCEG 6 ACC 27 BCEG 6 ACC 27 BCEG 6 ACC 28 BDEF 6 ACC 29 ACC 20 BDEF 6 ACC 20 BDEF 6 ACC 21 BCEG 6 ACC 20 BDEF 6 ACC 27 BCEG 6 ACC 27 BCEG 6 ACC 28 BDEF 6 ACC 29 ACC 20 BDEF 6 ACC 20 BDE	-11
DE 3-5 ACEF -40 DE -41 DE -50 DE -5	
BF 9 ACEG 21 BG -9 ACEG 21 BG -25 ACFG -32 FG -188 ADEF 7 ABC -21 ADEG -41 ABD 13 ADEG -1 ABE -6 AEFG -5 ABF 4 BCDE -56 ABF 4 BCDE -56 ACC -14 BCD -14 BCD -24 ACD -14 BCD -25 ACF -27 BCFG -6 ACG -27 BCFG -6 ACG -20 BDEF -6 ACG -20 BDEF -6 ACG -20 BDEF -6 ACG -20 BDEF -6 ACG -20 ACF -27 BCFG -6 ACF -27 ACFG -27 ACFG -27 ACFG -27 ACFG -32	
EF -9 ACFG -32 EG -25 ADEC -32 FG -188 ADEC -7 RG -188 ADEG -41 ABC -21 ADFG -1 ABD 13 AEFG -4 ABF -6 BCDE -56 ABF 1 BCDF 14 ACC 1 BCDF 14 ACC 1 BCCF -8 ACC -20 BCFG -6 ADF -17 BDEG 12 ADF -17 BDEG 12 ADF -17 BDEG 12 ADF -17 BDEG 12 ADF -33 BEFG -30 AEF -33 BEFG -30 AEF -53 BEFG -30 AEF -53 CDFF -19	
EG 1.58 ADEF 7 ABC 1.88 ADE 7 ABC 41 ADEG 41 ABC 41 ADEG -1 ABE 6 AEFG -1 ABF 4 BCDE -56 ABG 1 BCDF 24 ACD -14 BCDG 24 ACD -14 BCDG 29 ACF 27 BBCG 39 ACF 27 BBCG 39 ACF 27 BBCG 39 ACF 30 BDEF 6 ADE 30 BDEF 17 ACF -17 BDFG -32	
ABC	
ABD 13 ADFG -1 ABD 13 ADFG -1 ABF -6 AEFG -5 ABF -4 BCDE -56 ABG -1 BCDF -14 ACD -14 BCDG -24 ACE -1 BCCF -27 ACF -27 BCCF -29 ACF -27 BCCF -6 ADE -30 BDCF -6 ADE -30 BDCF -6 ADE -30 BDCF -6 ADE -31 BDCG -32 ADF -17 BDCG -32 ADF -17 BDCG -32 ADF -53 BEFG -30 ADF -51 CDFF -17 ADG -52	
ABE -6 AEFG 4 ABE -6 BCDE -56 ABR -1 BCDF 14 ACD -14 BCDF 24 ACE 1 BCEF -8 ACE 27 BCEG 6 ACG 20 BCFG 6 ADB -17 BDEG 12 ADB -17 BDEG 12 ADF -17 BDEG 12 ADF -53 BEFG 30 AEF -53 BEFG 30 AEF -53 CDFF 19	
ABF 4 BCDE -56 ABG 1 BCDF 14 AGCD -14 BCDG 24 ACCB 1 BCDG 29 ACCF 27 BCBG 29 ACCG -20 BCCG 6 ADE 30 BDEF 17 ADF -17 BDEG 12 ADF -17 BDEG 12 ADF -53 BEFG 30 ABF -53 BEFG 30 ABF -17 CDFF 19	
ABG 1 BCDF 14 ABG 24 ACD 14 BCEF -8 ACE 1 BCEG 29 ACC 20 BCFG 6 ADE 30 BDEF 6 ADE 30 BDEF 17 ADE 35 ADE 37	
ACD -14 BCDG 24 . ACD -14 BCEF -8 . ACF 1 BCBG 29 . ACF 27 BCFG 6 AOG -20 BDFF 6 ADE 30 BDFF 17 BDFG 12 ADF -17 BDFG 12 ADF -53 BEFG 30 AFF -53 EEFG 30 AFF -17 CDFF 19	
ACD -14 BCEF -8	
ACF 27 BCEG 29 : ACF 27 BCFG 6 ACG -20 BDFF 6 ADE 30 BDFF 6 ADF 17 BDFG 12 ADF -17 BDFG -32 ADF -53 BEFG 30 AFF 51 CDFF 19	
ACC	
ACG -20 BDEF 6 ADE 30 BDEG 12 ADF -17 BDFG -32 ADG -6 BDFG -32 AEF -53 BEFG 30 AFG 17 CDFF 19	
ADF 3.7 BDEG 12 ADF -1.7 ADF -3.2 ADF -2.5 BEFG 30 ADF -5.3 BEFG 30 ADF -5.1 CDFF 19	
ADG -6 BDFG -32 AEF -53 BEFG 30 AEF 17 CDEF 19	
ADG -0 BEFG 30 AEF -53 BEFG 17 CDEF 19	
AEG 17 CDEF 19	
AFG 55	
BCD -1005	
BCE -30	
BCF 14	
BCG 28	
BDE -10	
BDF 47	
BDG /	
BEF 36 ABCEG -34	

[0001] The Effects are fitted to a normal probability plot and four points are identified as falling outside two standard deviations of the straight line fit: D, G, FG, and BCD. The BCD interaction is identified as a potential lead to nonlinear behavior simultaneously involving the Cocatalyst Metal (B), the Cocatalyst Metal Amount (C),

and the Cosolvent (D). Repeated followup iterations identify a strong synergistic effect of high levels of Fe in the presence of THF.

[0001] While preferred embodiments of the invention have been described, the present invention is capable of variation and modification and therefore should not be limited to the precise details of the EXAMPLE. The invention includes changes and alterations that fall within the purview of the following claims.